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THE LINK BETWEEN GUT MICROBIOME, CYTOKINE PROFILE AND ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ESSENTIAL ARTERIAL HYPERTENSION

Vadym P. Shypulin, Vladyslav A. Tovstyha

Bogomolets National Medical University, Kyiv, Ukraine

Abstract

Introduction. Essential arterial hypertension is a major cause of cardiovascular morbidity and mortality. Recent studies highlight the gut microbiome's role in its development. This study assesses how gut microbiome composition affects blood pressure and endothelial dysfunction in hypertensive patients compared with healthy individuals.
Aim. To evaluate the influence of gut microbiome composition on blood pressure levels and its correlation with pro-inflammatory (interleukin-6, IL-6) and anti-inflammatory (interleukin-10, IL-10) cytokines in patients with essential arterial hypertension; to investigate changes in brachial artery diameter after limb ischemia in patients with essential arterial hypertension depending on gut microbiome composition and IL-6 and IL-10 levels, and to compare these indicators with a healthy control group.
Materials and methods. The study included 55 patients with essential hypertension and 20 healthy individuals. All underwent clinical examination and blood pressure measurement. Gut microbiome composition was analyzed, focusing on *Bacteroides*, Firmicutes, and the Firmicutes/Bacteroides ratio. Proportions of subjects with reduced levels of *Lactobacillus spp.* (<107), *Bifidobacterium spp.* (<109), *Prevotella spp.* (<1011), *Acinetobacter spp.* (<106), *Roseburia inulinivorans* (<1010), and *Faecalibacterium prausnitzii* (<108) were recorded. Cytokine levels (IL-6, IL-10) were measured. Endothelial function was assessed using flow-mediated dilation (FMD).
Results. Hypertensive patients had higher IL-6 and lower IL-10 levels than controls. Analysis revealed significant microbiome differences, with microbial imbalance potentially associated with inflammation and metabolic changes.
Conclusions. The study confirms the role of gut microbiome imbalance and cytokine dysregulation in hypertension. Microbiome alterations may contribute to pathogenesis. Further research should explore microbiome modulation as a potential therapeutic approach.

Keywords: **cardiovascular diseases, hypertension, gut microbiome, dysbiosis, cytokine, vascular endothelium**

INTRODUCTION

The gut microbiome (GM) plays a crucial role in maintaining the body's homeostasis by influencing various biological processes, including the development of cardiovascular diseases. Recent studies indicate a link between gut dysbiosis and systemic inflammation, which in turn may contribute to the development of essential arterial hypertension (EAH) and endothelial dysfunction. This study provides further insight into the mechanisms underlying hypertension, highlighting the importance of gut microbiome as a potential modulator in this process. The composition of the gut microbiome is primarily influenced by diet and eating habits, as these determine the supply of nutrients necessary for maintaining eubiosis – an optimal qualitative and quantitative state of the intestinal microbiome [1-2, 7].

Gut dysbiosis refers to an imbalance in the normal composition and function of the microbiome. This disruption can activate various molecular mechanisms that lead to systemic inflammation. In particular, increased intestinal permeability and the translocation of microbial products such as lipopolysaccharides (LPS) into the bloodstream trigger immune system activation and chronic inflammation.

This, in turn, is one of the main factors that may contribute to the development of arterial hypertension [3, 9-10].

Systemic inflammation is a key factor not only in disrupting normal cardiovascular function but also in provoking endothelial dysfunction. The endothelium, as the inner lining of blood vessels, is responsible for regulating vascular tone, interacting with blood cells, and maintaining normal blood pressure levels. Inflammation caused by dysbiosis can impair endothelial function, leading to the development of hypertension and other cardiovascular disorders [4-6, 8].

Moreover, recent research emphasizes the role of the GM in regulating various metabolic pathways that directly affect blood pressure. Thus, dysbiosis may be one of the main causes of disrupted homeostasis, involving both microbial and systemic mechanisms. Growing scientific evidence suggests that studying dysbiosis may be a key direction in understanding the mechanisms of essential arterial hypertension [11-13].

AIM

The aim of this study is to evaluate the influence of gut microbiome composition on blood pressure levels and its correlation with pro-inflammatory (interleukin-6, IL-6) and anti-inflammatory (interleukin-10, IL-10) cytokines in patients with essential arterial hypertension; to investigate changes in brachial artery diameter after limb ischemia in these patients depending on gut microbiome composition and IL-6 and IL-10 levels, and to compare these indicators with a healthy control group.

MATERIALS AND METHODS

The clinical study was conducted in accordance with the Law of Ukraine «On Medicinal Products», Good Clinical Practice (GCP) standards, and the ethical principles of the Declaration of Helsinki. The study was approved by the Bioethics and Research Ethics Committee of the Bohomolets National Medical University (Protocol No. 167 dated 21.11.2022) and was carried out at the clinical base of the Department of Internal Medicine No. 1 from 2022 to 2024. Written informed consent was obtained from all participants before enrollment.

The study included 55 patients with essential arterial hypertension aged 40 to 67 years. Inclusion criteria were: men and women aged 40-75 years with stage II, grade 1 or 2 essential arterial hypertension, patients not previously treated with antihypertensive therapy, and for women of reproductive age – a negative pregnancy test and signed informed consent.

Exclusion criteria included: stage III essential hypertension, chronic kidney disease stages III-V (eGFR <60 mL/min/1.73 m^2), endocrine disorders, office systolic BP <115 mmHg or diastolic BP <55 mmHg, atrial fibrillation or flutter, second- to third-degree AV block on ECG, NYHA class III-IV chronic heart failure, active inflammatory processes (CRP >10 mg/L), history of acute or chronic coronary syndrome, alcoholism, drug addiction, mental disorders, infectious diseases, oncological or hematological diseases, active gastrointestinal or liver diseases, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), IBS, renal artery stenosis, sarcoidosis, urolithiasis, tuberculosis, pregnancy, and lactation.

The use of the following medications was prohibited during the study: prebiotics, probiotics, antibiotics, and laxatives. Study participants were instructed to maintain a standard diet without significant changes throughout the study period.

The control group consisted of 20 healthy individuals with no history of hypertension, cardiovascular disease, diabetes mellitus, or other metabolic disorders, and who had not taken antihypertensive medications.

The mean age in the study group was 51.18 ± 7.12 years, and 47 ± 5.06 years in the control group. Systolic blood pressure (SBP) was 155 [148-159] mmHg and 128 [118-131] mmHg; diastolic blood pressure (DBP) was 95 [92-96] mmHg and 79 [82-68] mmHg in the study and control groups, respectively. The groups were comparable in terms of mean age (p = 0.018) and sex distribution (p = 0.850). Data are presented in Table 1.

Table 1

General Characteristics of the Study Groups

Parameter		Comparison groups		p
		Study group	Control Group	
Age, years		51,18±7,12	47±5,06	0,018
Sex, n (%)	male	28(51%)	9(45%)	0,850
	female	27(49%)	11(55%)	-
SBP, mmHg		155 [148-159]	128 [118-131]	<0,001
DBP, mmHg		95 [92-96]	79 [82-68]	<0,001
Firmicutes/Bacteroides ratio, (F/B ratio)		6,6 [5,2-7.9]	1,5 [1,1-2,7]	<0,001
Firmicutes spp., %		70 [62-74]	40 [36-53]	<0,001
Bacteroides spp., %		10,9 [8.6-13.9]	27 [20-33]	<0,001
Interleukin-6 (IL-6), pg/mL		1,96 [1,74-2,22]	0,86 [0,8-0,95]	p<0,001
Interleukin-6 (IL-10), pg/mL		3,7 [2,88-4,74]	4,25 [3,15-5,2]	0,163
FDM, %		7 [5-10]	10,5 [8-13,5]	p<0,001

All patients from the study and control groups underwent analysis of the main types of gut microbiome: *Bacteroides*, Firmicutes; the proportion of patients with decreased levels of *Lactobacillus* spp. (<10^7), *Bifidobacterium* spp. (<10^9), *Prevotella* spp. (<10^11), *Acinetobacter* spp. (<10^6), *Roseburia inulinivorans* (<10^10), *Faecalibacterium prausnitzii* (<10^8) was determined, and the Firmicutes/Bacteroides ratio (F/B ratio) was evaluated.

Sampling for the analysis in the study group was carried out prior to the initiation of antihypertensive therapy to avoid drug-related effects on the gut microbiome. Sample collection and storage were conducted according to the protocol developed by the «Diagen» laboratory.

Real-time polymerase chain reaction (PCR) was performed at the «Diagen» laboratory using the Rotor-Gene 6000 thermal cycler (Qiagen, Germany). Serum interleukin-6 (IL-6) and (interleukin-10) IL-10 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA) in accordance with the manufacturer's instructions. Detection limits: IL-6-0.2 pg/mL, IL-10-0.1 pg/mL.

Endothelium-dependent dilation (flow-mediated dilation, FMD) of the brachial artery was assessed by duplex ultrasound (GE Vivid S60, probe 7.5-12 MHz). Reactive hyperemia was induced by inflating a cuff on the upper arm for 5 minutes. Measurements were taken before compression and 60 seconds after release. FMD (%) was calculated as the percentage change in artery diameter compared to the baseline value.

Statistical analysis was performed using EZR software version 2.8 (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for the R software package (The R Foundation for Statistical Computing, Austria). Wilcoxon's W test was used to compare quantitative data, and Fisher's exact test (with Yates' correction) was used to compare categorical data (i.e., frequency of deviations from laboratory norms). Normality of distribution was checked using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation; non-normally distributed data are presented as median and interquartile range.

RESULTS

Systolic blood pressure (SBP) in the study group was significantly higher (155 [148-159] mmHg) compared to the control group (128 [118-131] mmHg), $p < 0.001$. Diastolic blood pressure (DBP) was also significantly higher in the study group (95 [92-96] mmHg) than in the control group (79 [68-82] mmHg), $p < 0.001$.

Gut microbiome composition showed a markedly elevated Firmicutes/Bacteroides ratio in the study group – 6.6 [5.2-7.9], compared to the control group – 1.5 [1.1-2.7], $p < 0.001$. The proportion of *Firmicutes* spp. in the study group was 70 [62-74] % and was significantly higher than in the control group (40 [36-53] %), $p < 0.001$. Conversely, the proportion of *Bacteroides* spp. was significantly lower in the study group (10.9 [8.6-13.9] %) than in the control group (27 [20-33] %), $p < 0.001$.

A comparison of the pro-inflammatory cytokine IL-6 levels showed a significantly higher concentration in the study group (1.96 [1.74-2.22]) than in the control group (0.86 [0.80-0.95]), $p < 0.001$ – more than a twofold difference.

The anti-inflammatory cytokine IL-10 did not show statistically significant differences between the study group (3.7 [2.88-4.74]) and the control group (4.25 [3.15-5.2]), $p = 0.163$. The change in brachial artery diameter (flow-mediated dilation, FMD) before and after limb ischemia, according to duplex ultrasound, was significantly lower in patients in the study group (7 [5-10] %) than in the control group (10.5 [8-13.5] %), $p < 0.001$.

Based on the correlation analysis, several statistically significant associations were identified. Notably, a moderate positive correlation was observed between IL-6 and systolic blood pressure ($r = 0.474$, $p < 0.001$), and a weak positive correlation with diastolic blood pressure ($r = 0.268$, $p = 0.0479$) (Table 2).

Additionally, there was a moderate positive correlation between IL-6 and the Firmicutes/Bacteroides (F/B) ratio ($r = 0.517$, $p < 0.001$), as well as a moderate negative correlation with the *Bacteroides spp.* proportion ($r = –0.527$, $p < 0.001$) (Table 2).

Table 2

Correlation Analysis of Parameters

Parameter	IL-6	IL-10	FDM
SBP	0.474	-	-
DBP	0.268	-	-
F/B ratio	0.517	-	-0.559
Firmicutes spp.	-	-	-
Bacteroides spp.	-0.527	-	0.643
IL-10	-0.29	-	-
FDM	-0.43	-	-

Note: Only statistically significant correlations (Pearson's correlation coefficients) ($p<0.05$) are presented.

DISCUSSION

The results obtained confirm the existence of an association between gut microbiome dysbiosis, changes in cytokine profile, and endothelial dysfunction in patients with essential arterial hypertension (EAH). The established significant increase in the Firmicutes/Bacteroides (F/B) ratio in patients with EAH is consistent with previous studies, in which an elevated value of this index was considered a marker of dysbiosis and metabolic disturbances [12, 13]. An excessive proportion of *Firmicutes* may potentially be associated with increased production of short-chain fatty acids, particularly acetate, which, as previously shown, contributes to elevated blood pressure through activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [3].

A decrease in *Bacteroides*, on the contrary, may reduce butyrate production – a metabolite with anti-inflammatory properties that supports endothelial integrity [4, 9]. The identified positive correlation between *Bacteroides* concentration and flow-mediated dilation (FMD) confirms the hypothesis of these bacteria's involvement in maintaining normal vascular tone.

Significantly elevated IL-6 levels in patients with EAH were accompanied by reduced endothelial-dependent dilation and positively correlated with systolic and diastolic blood pressure, aligning with existing data on the pro-atherogenic and vasoconstrictive effects of this cytokine [9]. IL-6 may suppress nitric oxide synthesis in the endothelium, promoting vascular dysfunction [9]. The negative correlation between IL-6 and IL-10 levels indicates an imbalance between pro- and anti-inflammatory mechanisms. IL-10 is known to have a protective effect on the vascular wall by inhibiting the expression of adhesion molecules and the production of reactive oxygen species [9].

Thus, the results suggest that gut microbiome dysbiosis may be one of the factors contributing to endothelial dysfunction through a mediated immune-inflammatory response. The established correlations do not allow us to draw causal conclusions, but they underscore the potential pathophysiological role of the microbiome in the development of hypertension.

A limitation of the study is the small sample size, lack of stratification by hypertension stage, and the absence of an assessment of dietary influence, physical activity, or antihypertensive medication use on the microbiome. Further studies should include larger cohort samples, longitudinal observation, and interventional approaches (e.g., probiotic or prebiotic supplementation) to confirm the proposed hypotheses.

CONCLUSIONS

Patients with essential arterial hypertension show alterations in gut microbiome composition associated with higher blood pressure levels. In particular, an increased relative abundance of Proteobacteria and reduced microbial diversity were linked to higher systolic and diastolic blood pressure values. A higher proportion of conditionally pathogenic bacteria in the gut microbiome was associated with elevated levels of the pro-inflammatory cytokine IL-6 and reduced levels of the anti-inflammatory cytokine IL-10. This indicates the involvement of the microbiome in the formation of a systemic inflammatory state, which may influence the pathogenesis of arterial hypertension. Patients with essential hypertension exhibited impaired flow-mediated dilation of the brachial artery following ischemia, indicating endothelial dysfunction. The severity of this impairment was associated with gut microbiome dysbiosis and elevated IL-6 levels. Compared to the control group of healthy individuals, patients with hypertension had higher IL-6 levels, lower IL-10 levels, impaired vascular reactivity, and significant differences in microbiome composition, supporting the association between the microbiome, cytokine profile, endothelial dysfunction, and arterial hypertension.

Perspectives for further research. Future research should focus on a more detailed study of the mechanisms linking gut microbiome composition, its metabolites, and systemic hemodynamics in patients with essential arterial hypertension. It would be advisable to expand future studies by including larger samples, investigating genetic polymorphisms that affect immune responses and microbiome metabolism, and developing personalized probiotic interventions based on the patient's baseline microbiome profile.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The clinical study was conducted in accordance with the Law of Ukraine «On Medicinal Products,» the requirements of Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. The study was approved by the Bioethics and Ethics Committee for Scientific Research at Bogomolets National Medical University, Protocol No. 167 dated 21.11.2022. Written informed consent was obtained from all participants prior to the study.

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This study was self-funded. The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Shypulin V. P.[A, B, E, F]

Tovstyha V. A.[A, B, C, D, E, F]

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Резюме

ЗВ'ЯЗОК МІЖ КИШКОВИМ МІКРОБІОМОМ, ПРОФІЛЕМ ЦИТОКІНІВ ТА ЕНДОТЕЛІАЛЬНОЮ ДИСФУНКЦІЄЮ У ПАЦІЄНТІВ З ЕСЕНЦІАЛЬНОЮ АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

Вадим П. Шипулін, Владислав А. Товстига

Національний медичний університет імені О. О. Богомольця, м. Київ, Україна

Вступ. Есенціальна артеріальна гіпертензія є основною причиною серцево-судинної захворюваності та смертності. Нещодавні дослідження підкреслюють роль кишкового мікробіому в його розвитку. Це дослідження оцінює, як склад кишкового мікробіому впливає на артеріальний тиск та ендотеліальну дисфункцію у пацієнтів з гіпертензією порівняно зі здоровими людьми.

Мета. Оцінити вплив складу кишкового мікробіому на рівень артеріального тиску та його кореляцію з прозапальними (інтерлейкін-6, IL-6) і протизапальними (інтерлейкін-10, IL-10) цитокінами у пацієнтів з есенціальною артеріальною гіпертензією; дослідити зміни діаметра плечової артерії після ішемії кінцівки у пацієнтів з есенціальною артеріальною гіпертензією залежно від складу кишкового мікробіому та рівнів ІЛ-6 і ІЛ-10, а також порівняти ці показники з групою здорових осіб.

Матеріали та методи. У дослідження було включено 55 пацієнтів з есенціальною артеріальною гіпертензією та 20 здорових осіб. Усі учасники пройшли клінічне обстеження та вимірювання артеріального тиску. Було проаналізовано склад кишкової мікробіоти з акцентом на Bacteroides, Firmicutes та Firmicutes/Bacteroides співвідношення (F/B співвідношення). Визначалися частки учасників зі зниженим рівнем *Lactobacillus* spp. (<107), *Bifidobacterium* spp. (<109), *Prevotella* spp. (<1011), *Acinetobacter* spp. (<106), *Roseburia inulinivorans* (<1010) і *Faecalibacterium prausnitzii* (<108). Вимірювалися рівні цитокінів (ІЛ-6, ІЛ-10). Функцію ендотелію оцінювали за допомогою тесту на ендотелійзалежну вазодилатацію.

Результати. У пацієнтів з гіпертензією рівень ІЛ-6 був вищим, а рівень ІЛ-10 нижчим, ніж у контрольній групі. Аналіз виявив значні відмінності в мікробіомі, причому мікробний дисбаланс потенційно пов'язаний із запаленням та метаболічними змінами.

Висновки. Дослідження підтверджує роль дисбалансу кишкового мікробіому та порушення регуляції цитокінів у патогенезі артеріальної гіпертензії. Зміни в мікробіомі можуть бути важливим фактором розвитку захворювання. Подальші дослідження мають бути зосереджені на можливостях модифікації мікробіому як потенційної терапевтичної стратегії.

Ключові слова: **серцево-судинні захворювання, гіпертензія, кишковий мікробіом, дисбіоз, цитокіни, ендотелій судин**

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